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Design and Development of Effervescent Floating Tablet Dapagliflozin

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ABSTRACT

The objective of the present study was to formulate and evaluate Effervescent Floating Tablet of Dapagliflozin for the treatment of antidepressant agent. Tablets were prepared by direct compression using directly compressible polymers such as HPMC K4M, and Carbopol 934 were evaluated for drug-excipient compatibility, density, buoyancy test, swelling study, drug content and In-Vitro release profile. Sodium bicarbonate and citric acid were used producing effervescent base for buoyancy of tablets. Analysis of drug release from tablet indicates drug release by zero order, first order rate kinetics. No significant change was observed in physical appearance, drug content, floatability or in-vitro dissolution pattern after storage at 450C/750C RH for three months.

KEYWORDS: *Floating effervescent tablet, GIT, Dapagliflozin, HPMC K4M, Carbopol 934*

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INTRODUCTION

Oral drug administration still remains the route of choice for the majority of clinical applications some drug have ideal characteristics for good absorption to occur desirable for optimizing the therapeutic benefit of the drug[1]. Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation[2]. Attempts have been made to be 8-10 hr. From mouth to colon, is relatively brief with considerable fluctuation. One of the important determinants of G.I transit is the residence time in the stomach. The oral controlled delivery of drugs having "absorption window" continually releasing the drug prior to absorption window for prolonged period of time, thus ensuring optimal bioavailability[3]. A floating dosage unit is useful for drugs acting locally in the proximal gastrointestinal tract. These systems are also useful for drugs that are poorly soluble or unstable in intestinal fluids. Floating tablets and Floating capsules are common examples of floating system[4,5].

Effervescent Floating Drug Delivery System:

A gastro retentive dosage form will release the drug over an extended period in the stomach and upper gastrointestinal tract (GIT) thus enhancing the opportunity for absorption.

Various approaches have been proposed to control the gastric residence of drug delivery system in the upper part of the GIT including floating drug delivery system. High density DDS, bioadhesive systems, swelling and expanding DDS, modified shape systems and other delayed gastric devices[5,6]. FDDS is suitable for drugs with an absorption window in the stomach or the upper small intestine, for drugs which act locally in the stomach and for drugs that are poorly soluble or unstable in the intestinal fluid DDS or hydro dynamically balanced systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Based on the mechanism of buoyancy, two distinctly different technologies, *i.e.* non-effervescent and effervescent systems, have been used in the development of FDDS[6,7,8].

The effervescent system uses matrices prepared with swellable polymers and effervescent components *e.g.* sodium bicarbonate and citric acid or stearic acid. In non-effervescent FDDS, the drug mixes with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration to maintain a relatively stable shape and a bulk density of less than unity within the outer gelatinous barrier[9].

MATERIAL AND METHOD

MATERIAL

Preformulation Study of Drug:

Preformulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug

substance, alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass-produced[10,11].

Identification Tests

Organoleptic Properties:

The sample of Dapagliflozin was studied for organoleptic characteristics such as colour, odour and appearance[10,11].

Melting Point:

Melting point of Dapagliflozin was determined by taking a small amount of sample in a capillary tube closed at one end and placed in melting point apparatus. The melting point was noted in triplicate and average value was noted[10,11].

IR Spectroscopy

The FT-IR spectrum of the obtained sample of drug was compared with the standard FT-IR spectra of the pure drug.

Solubility analysis:

Preformulation solubility analysis was done to select a suitable solvent system to dissolve the drug and also to test its solubility in the dissolution medium which was to be used.

Differential Scanning Calorimetry:

The powdered sample (3 mg) was hermetically sealed in aluminium pans and heated at a constant rate 10^0C/min, over a temperature range of 30-300^{0}C with nitrogen flow rate of 30ml/min. Thermograms of the samples were obtained using differential scanning Calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded with Shimadzu software programs. Indian standard was to calibrate the DSC temperature and enthalpy scale.

Table No 2: Formulation Chart of Effervescent Floating Tablet of DAPAGLIFLOZIN

Ingredients	Formulation code								
Quantity (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dapagliflozin	5	5	5	5	5	5	5	5	5
HPMC K4M	50	50	50	60	60	60	70	70	70
Carbopol 934	10	15	20	10	15	20	10	15	20
Sodium Bicarbonate	30	30	30	30	30	30	30	30	30
Citric acid	10	10	10	10	10	10	10	10	10
Mg Stearate	3	3	3	3	3	3	3	3	3
Lactose	47	42	37	37	32	27	27	22	17
Total Weight	155	155	155	155	155	155	155	155	155

Determination of Swelling Index:

The swelling properties of matrices containing drug were determined by placing tablet matrices in the dissolution test apparatus in 900 ml 0.1 N HCl at 37 ± 0.5^{0}C. The tablets were removed periodically from the dissolution medium and, after removing free water, the weight gain was measured. The swelling characteristics were expressed in terms of the percentage water uptake (WU %) according to the equation[5].

Determination of Floating capacity:

Three individual tablets from each formulation were put in an individual flask containing 400ml of 0.1 N HCl solutions. Then note time in minutes for each tablets to go from the bottom to the top of the flask (floating lag time) and the time for which tablets constantly float on the water surface (duration of floating) were measured. The sample mean and standard deviation were calculate preparation complies with the test, only if each individual content lies between 85 to 115% of the average content[4].

***In Vitro* drug release kinetics studies**

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero orders, first order, Higuchi square root, korsmeyer peppas model.

RESULT &DISCUSSION

Preformulationstudy:

OrganolepticProperties:

Table: Organoleptic Properties of Dapagliflozin

Identification test	Result of sample obtained	Reported standards
Colour	White	White
Odour	Odourless	Odourless
Melting point	65-70°C	69°C

All the physical properties of the drugs were within the limit of reported standards which assures the purity of the drug samples.

Solubility:

Solubility in different solvents

Sr. no	Solvent	Observation
1	Water	soluble
2	Methanol	soluble
3	0.1 N HCl	soluble

Ultraviolet - Visible Spectroscopy Study

Determination of λ_{max} in methanol:

Solutions of Dapagliflozin was prepared in Methanol and scanned between 400-200 nm using UV spectrophotometer showed peak at wavelength 230 nm. However, keeping in mind the probable concentrations likely to be encountered while carrying out *In- vitro* release studies and considering the predicted theoretical λ_{max} involved, the working λ_{max} was decided as 230 nm as shown in figure 12.

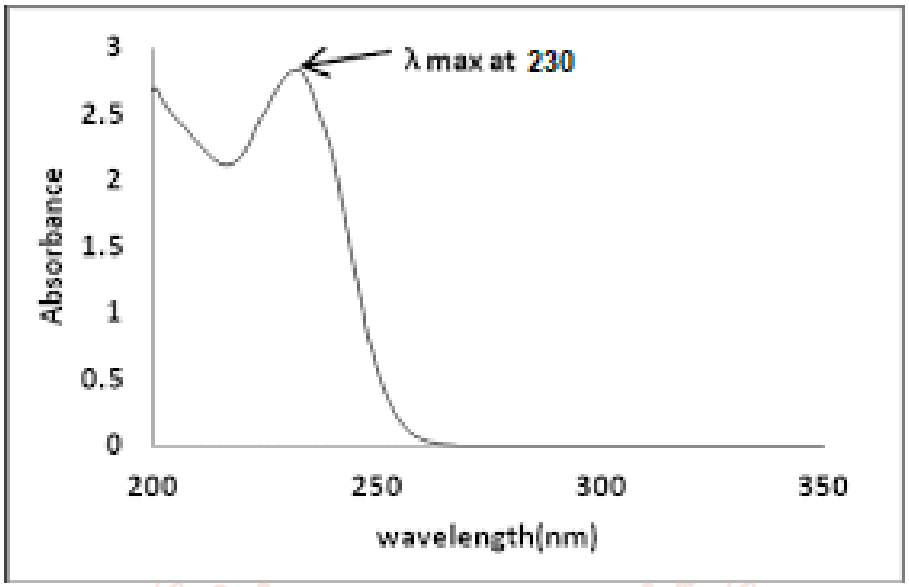

Figure: UV-Visible spectrum of Dapagliflozin in Methanol

Preparation of calibration curve in Methanol:

Calibration curve of Dapagliflozin was performed in methanol as Dapagliflozin is freely Soluble methanol solution of drug was very clear and readily analyzed by UV spectrophotometer. The calibration curve was found to be linear in the concentration range of 5-25µg/ml and coefficient of regression value R^2 =0.9991 and Slope y = 0.0475x - 0.0913 The calibration curve of Dapagliflozin in methanol is shown in Figure 12 and absorbance of Dapagliflozin in methanol at 230 nm is shown in Table 17.

Table: Absorbance of Dapagliflozin in Methanol at 230nm

Sr. No.	Concentration(ppm)	Absorbance
1	5	0.1602
2	10	0.3721
3	15	0.6116
4	20	0.8561
5	25	1.1056

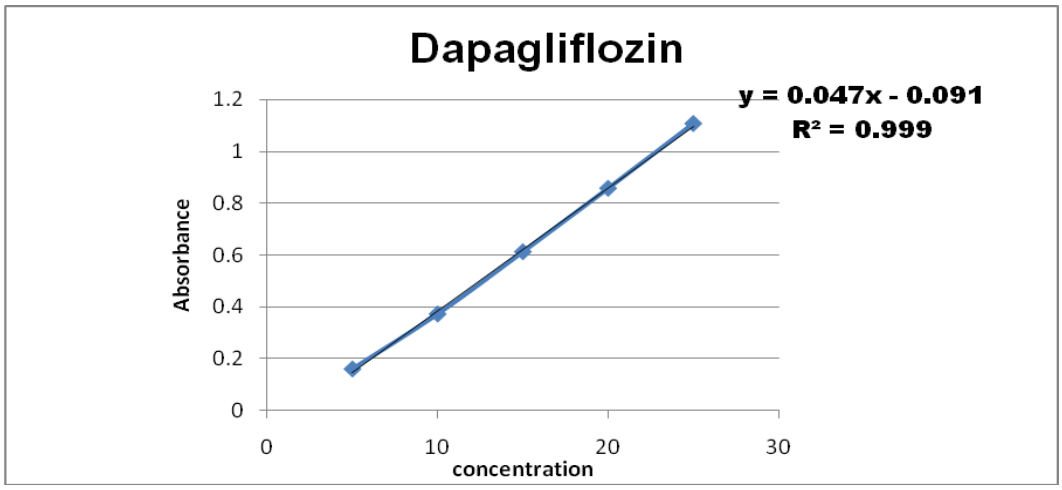

Figure: Calibration curve of Dapagliflozin in Methanol

Compatibility study:

Infra-Red Spectrum of Dapagliflozin

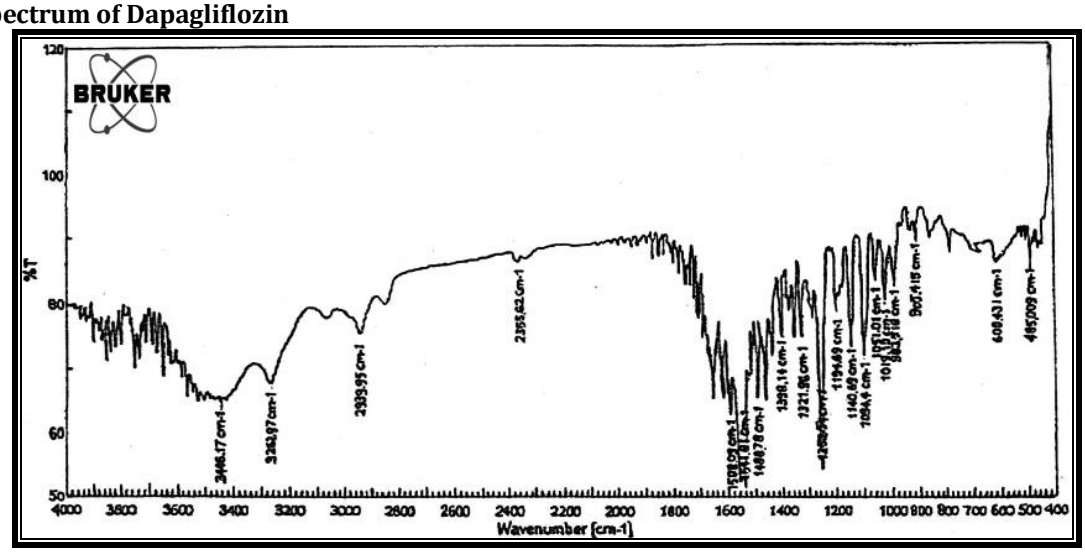

Figure .FTIR Spectrum of Dapagliflozin

The FTIR spectra of pure Dapagliflozin showed the peaks at wave numbers (cm^{-1}) which correspond to the functional groups present in the structure of the drug.

Table: Ranges of the functional groups present in I.RDapagliflozin

Sr. No.	Functional Groups	Observed Ranges (cm^{-1})	Standard Ranges (cm^{-1})
1.	C-Cl stretching	608	600-800
2.	O-H stretching	3446.17	3700-3100
3.	C-C stretching	1263.12	1290-1299
5.	C-O stretching	1140.69	1150-1165
6.	C-H stretching	1064.4	1055-1065
7.	C-H stretching	1019.15	1008-1035
8.	C-H_2 rocking	805.41	862-870

Absorption bands shown by Dapagliflozin were characteristic of the groups present in its molecular structure. The presence of absorption bands corresponding to the functional groups present in the structure of Dapagliflozin the absence of any well-defined uncountable peak is a confirmation of the purity of the drug sample.

Fourier Transform Infrared Spectroscopy:

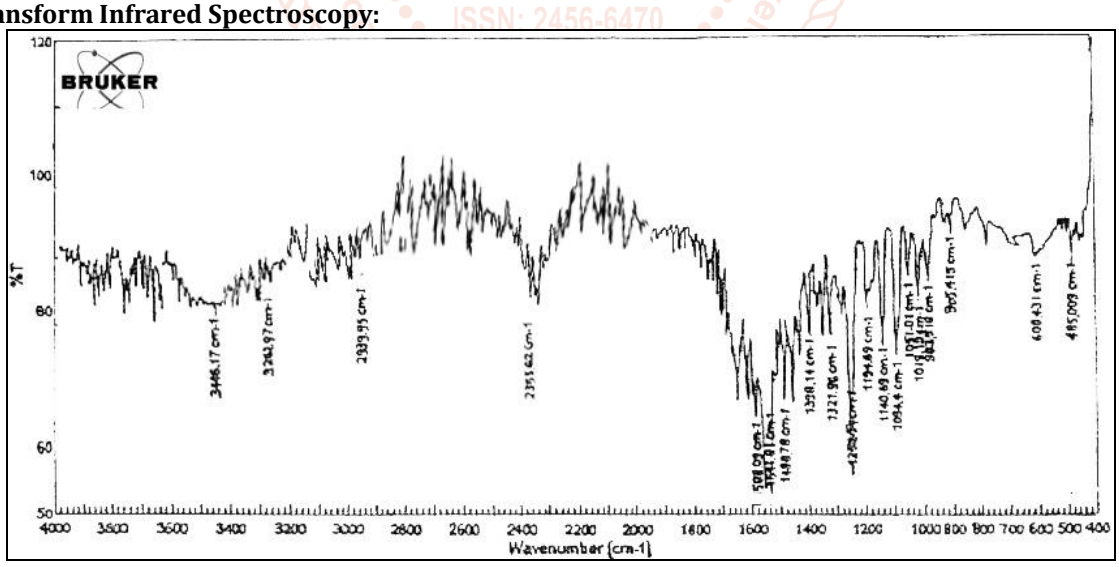

Figure: IR Spectrum of Physical mixture of Drug and Excipient

Table: Interpretation of IR spectra physical mixture of Dapagliflozin and Excipients

Functional group	Peaks	
	Pure drug	Physical mixture
C=O stretching	Yes	Yes
C-H streching	Yes	Yes
C-Cl stretching	Yes	Yes
C-O stretching	Yes	Yes
C-H stretching	Yes	Yes
C-H stretching	Yes	Yes

.Differential Scanning Calorimetry:-

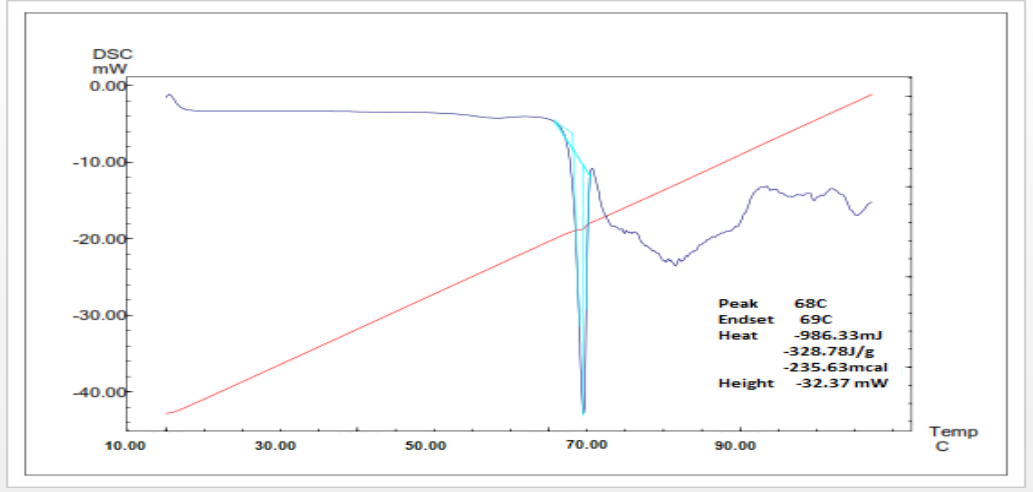

Figure 15: DSC Thermogram of Dapagliflozin

Table: DSC Thermogram of Dapagliflozin was interpreted.

DSC Analysis	
Reported Standard in literature	Observed
65-70^{0}C	69^{0}C

The DSC curve of Dapagliflozin showed a sharp endothermic peak at 69^{0}C corresponding to its melting, which confirm that purity of the drug. The drug did not decomposition followed by its melting.

Evaluation of Pre-compressed Parameters:

All formulations were studied for various rheological characteristics bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. The results of the studies indicated that the powder is blend is easily compressible.

Table: Pre-Compressed Evaluations

Formulation code	Bulk density (gm/ml)	Tapped density (gm/m)	Angle of Repose (θ)	Compressibility index (%)	Hausner's ratio
F1	0.369±0.0054	0.454±0.0014	28.56±0.51	9.45±0.32	1.14±0.025
F2	0.391±0.0002	0.432±0.0076	24.89±0.04	15.98±0.08	1.96±0.015
F3	0.313±0.0023	0.419±0.0012	27.23±0.19	12.33±0.21	1.91±0.032
F4	0.329±0.0010	0.452±0.0029	19.33±0.92	20.63±0.36	1.10±0.039
F5	0.319±0.0029	0.429±0.0093	23.34±0.29	8.28±0.22	1.02±0.020
F6	0.376±0.0073	0.492±0.0098	19.38±0.21	14.33±0.46	1.87±0.043
F7	0.312±0.0032	0.439±0.0098	25.66±0.49	9.42±0.58	1.94±0.093
F8	0.325±0.0005	0.488±0.0058	20.44±0.39	20.85±0.47	1.37±0.027
F9	0.352±0.0025	0.468±0.0078	23.78±0.79	14.76±0.24	1.84±0.089

Angle of repose between 25^0 to 30^0 indicates excellent Flowability of powder bed. In this work, the angle of repose was found to be varying between 19.33 and 28.56 when glidants were incorporated. These studies indicated that, the powder beds of all formulations are easily flowable**.**

.Evaluation of Post Compressed Characteristics:

The results of Hardness, Disintegration time, Drug content, Friability, Swelling index, Floating time all are summarized in the table given below:

Table Post-Compressed Evaluations

Formulation code	Hardness (kg/cm^2) ± S.D.	Drug content (%) ± S.D.	(%) Friability ± S.D.	Swelling index %	Thickness (mm)	Weight Variation (mg)
F1	3.34±0.054	95.34±0.024	0.253±0.022	42.25±0.53	3.24 ±0.54	223.42± 0.53
F2	3.25±0.064	98.32±0.053	0.294±0.064	38.33±0.56	3.95±0.34	224.42±0.53
F3	3.35±0.025	99.35±0.062	0.324±0.034	46.35±0.25	3.62±0.25	223.62±0.62
F4	3.22±0.062	100.15±0.02	0.362±0.085	46.36±0.36	3.83±0.62	225.36±0.036
F5	3.62±0.022	99.52±0.092	0.362±0.062	49.25±0.25	3.24±0.62	223.62±0.926
F6	3.73±0.073	101.52±0.03	0.325±0.073	48.25±0.62	3.73±0.62	223.42±0.251
F7	3.37±0.032	99.62±0.051	0.563±0.063	44.54±0.51	3.52±0.68	225.67±0.063
F8	3.73±0.783	95.37±0.073	0.473±0.77	48.22±.1.61	3.62±0.36	223.6 ± 0.062
F9	3.83±0.737	100.36±0.063	0.537±0.42	48.45±0.23	3.62±0.26	223.66±0.25

The tablets were evaluated for hardness, thickness, drug content uniformly, swelling index. These studies indicated that, Tablets of all formulations are easily flow able.

.In-*Vitro* Floating duration

Table: Floating duration time and Floating lag time

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Floating time (hr.)	12	12	12	12	12	12	12	12	12
Floating lag time (sec)	57	65	85	112	130	156	171	217	232

.In Vitrodrug release studies:

The dissolution studies were carried out for all nine formulations (i.e. F1 to F9)

Table: Percent Cumulative drug release of different Formulations (F1-F9)

Time (hr.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	6.36±1.98	6.64±5.95	7.57±2.15	9.12±2.42	7.78±2.06	8.84±1.90	8.06±2.02	4.90±2.10	5.70±1.53
2	17.29±2.38	21.68±1.93	19.27±2.25	15.79±1.74	16.43±2.83	16.67±2.32	15.58±4.11	10.15±2.04	10.57±2.08
3	25.42±2.06	27.57±1.83	25.14±2.05	25.34±2.31	19.06±1.99	23.18±2.501	17.46±2.05	19.25±2.07	12.86±2.84
4	35.88±2.52	31.58±2.54	32.99±2.21	31.70±1.58	21.81±2.61	29.81±2.49	18.03±2.56	24.45±2.83	23.46±2.01
5	39.84±1.87	39.84±2.22	40.14±1.94	42.31±2.41	25.34±1.91	36.72±1.92	22.24±1.93	30.41±1.95	30.41±1.90
6	46.40±2.02	48.55±2.39	48.55±2.11	47.24±2.15	28.29±2.15	38.05±1.9	33.08±2.07	37.90±1.90	39.25±1.89
7	55.16±2.10	57.31±2.62	57.39±1.99	53.01±1.94	31.84±1.95	45.69±2.34	36.87±2.00	45.43±1.43	47.58±4.95
8	61.10±2.04	65.66±2.19	68.37±2.04	62.00±2.17	43.97±2.06	49.72±2.06	45.22±2.15	53.01±2.11	50.86±2.47
9	64.98±2.07	73.26±2.04	75.24±2.54	69.41±2.00	54.99±2.00	65.32±1.98	53.29±2.01	62.43±1.92	55.16±1.81
10	71.44±2.64	80.21±2.03	82.71±2.36	76.94±1.86	64.87±1.63	76.74±2.45	65.36±2.56	70.44±1.36	59.30±1.56
11	76.73±2.42	79.53±2.69	86.63±1.96	79.53±2.62	82.36±1.25	83.18±2.48	70.61±2.00	75.90±2.33	65.37±2.06
12	79.53±2.48	84.48±2.09	96.35±2.08	81.72±2.08	89.63±1.98	88.82±2.63	87.43±2.53	77.87±1.88	69.97±1.32

The drug release shows that as the concentration of polymer goes on incresing the drug release also goes on decreasing and as well as time for drug release will be more sustained or release time will also goes on increasing, but we want more and optimize release at 12 hrs., it was shown by F3 batch 96.35 ±2.08. Hence, F3 batch was taken as optimize batch due to highest drug release up to 12hrs.

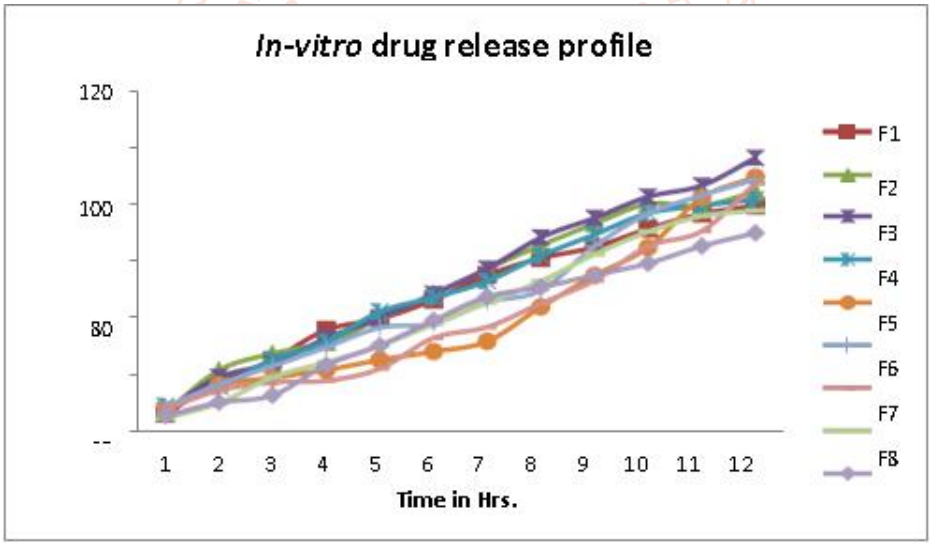

Figure: Dissolution Profile of Formulation Batches (F1-F9) (Time Vs %CDR)

F3 and Marketed Formulation

Table: % Cumulative drug release of F3 and Marketed Formulation(Farxiga SR)

Time (hrs.)	% drug release	
	F3 Batch	Marketed formulation
1	7.57	5.54
2	19.27	11.63
3	25.14	20.69
4	32.99	26.96
5	40.14	34.42
6	48.55	50.58
7	57.39	56.31
8	68.37	55.25
9	75.24	66.44
10	82.71	77.13
11	86.63	82.29
12	96.35	87.68

Optimization

A 3^2 full factorial design was selected and the 2-factors were evaluated at 3 levels, respectively. The percentage of HPMC K4M (X_1), and Carbopol (X_2) were selected as independent variables and the dependent variable was % drug release,The data obtain were treated using design expert version 11.0.0. Software and analysed statistically using analysis of variance (ANOVA). The data was subjected to 3-D response surface methodology to study effect of HPMC K4M (X_1) and carbopol (X_2) on dependent variable. Table 29 shows other statistical parameter for the dependent variable % drug released, The values of X_1 and X_2 were found significant at $p<0.0177$, hence conformed the significant effect of both the variable on selective responses. Form the data optimized concentration of HPMC K4M 70 mg and carbopol 20 mg was found. Multiple regression analysis of 3^2 full factorial design batches for *in-vitro* drug release, are show in table 28, 29 respectively**.**

Table: Multiple regression analysis for % drug release

Source	Sum of Squares	Degree of Freedom	Mean Square	F value	P-value	Inference
Model	405.65	3	138.24	9.23	0.0172	Significant
A-HPMC K4M	102.91	1	102.82	7.13	0.0446	
B-Carbopol 934	6.92	1	6.92	0.42	0.5216	
Residual	73.34	5	14.62			
Core total	479.04	8				

Final Equation in term of Actual factor:

Y1 (%CDR) = 0.06201 *(A) + 0.11751*(B)

Table: Other statistical parameter for % drug release.

Standard deviation	R-Squared	% CV	Mean	Press	Adequate Precision
1.98	0.9167	2.66	85.04	52.68	14.241

The variance inflation factor (VIF) measured how much the variance of the model coefficient was inflated by the lack of orthogonality in the design and was calculated for % drug released, Swelling index. It was found to be near one indicating good estimation of the coefficient. Similarly R-Squared was near to zero which lead to good model. The valuae of prob>F were less than 0.05, which indicated model term were significant. The linear model obtain from the regression analysis used to build up A 3-D graph in which the responses were represented by curvature surface as a function of independent variables can be directly visualized from the response surface plot. The response surface plot is generated using design expert 11.0.0. software represent in figure 19,20 to observed the effect of independent variable on the repose studied % drug released, swelling index. From response surface level 3 factorial design was chosen using linear designmode.

A. Surface Response Plots:

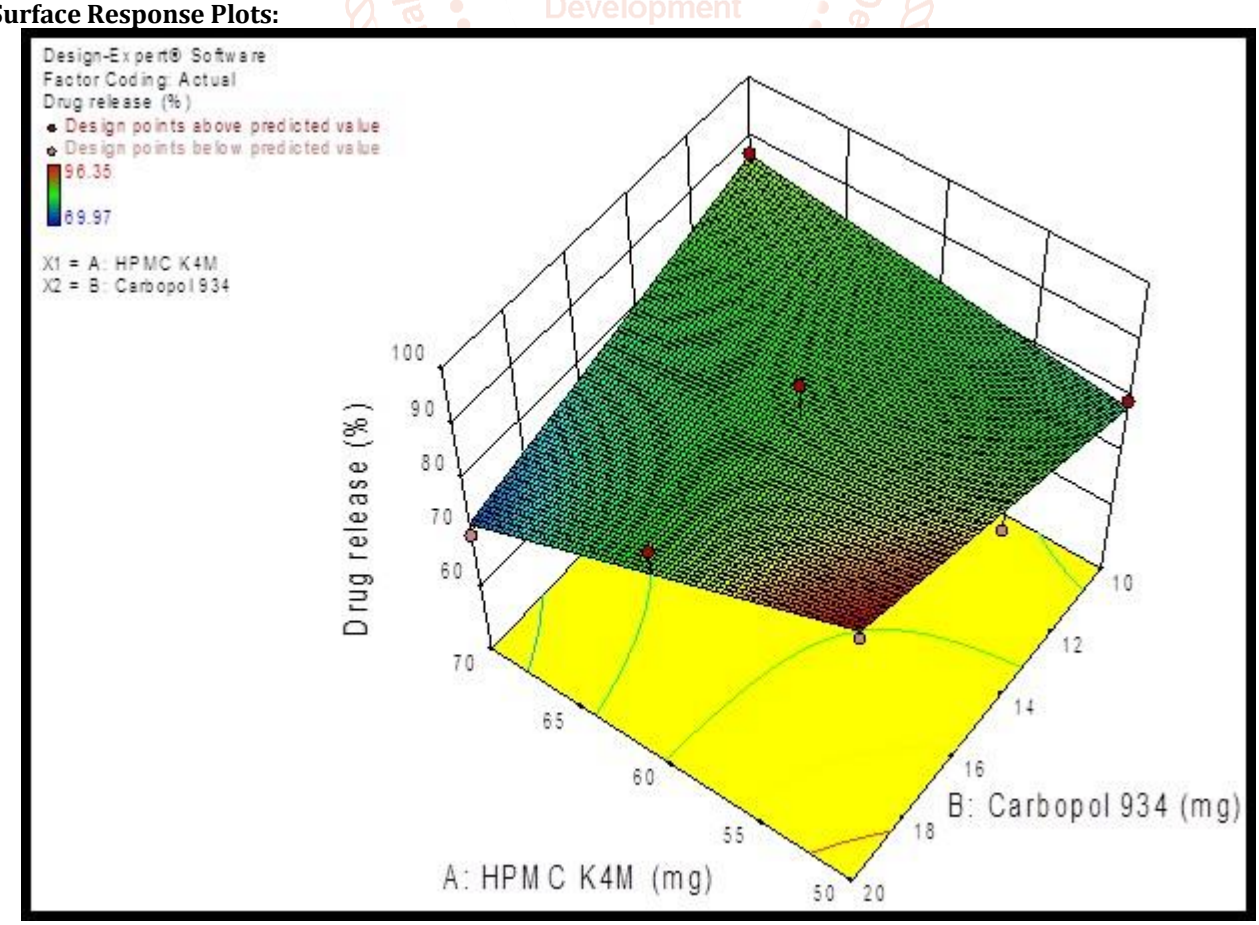

Figure: Surface Response plot showing effect of Carbopol 934 and HPMC K4M on drug release

Contour plot:

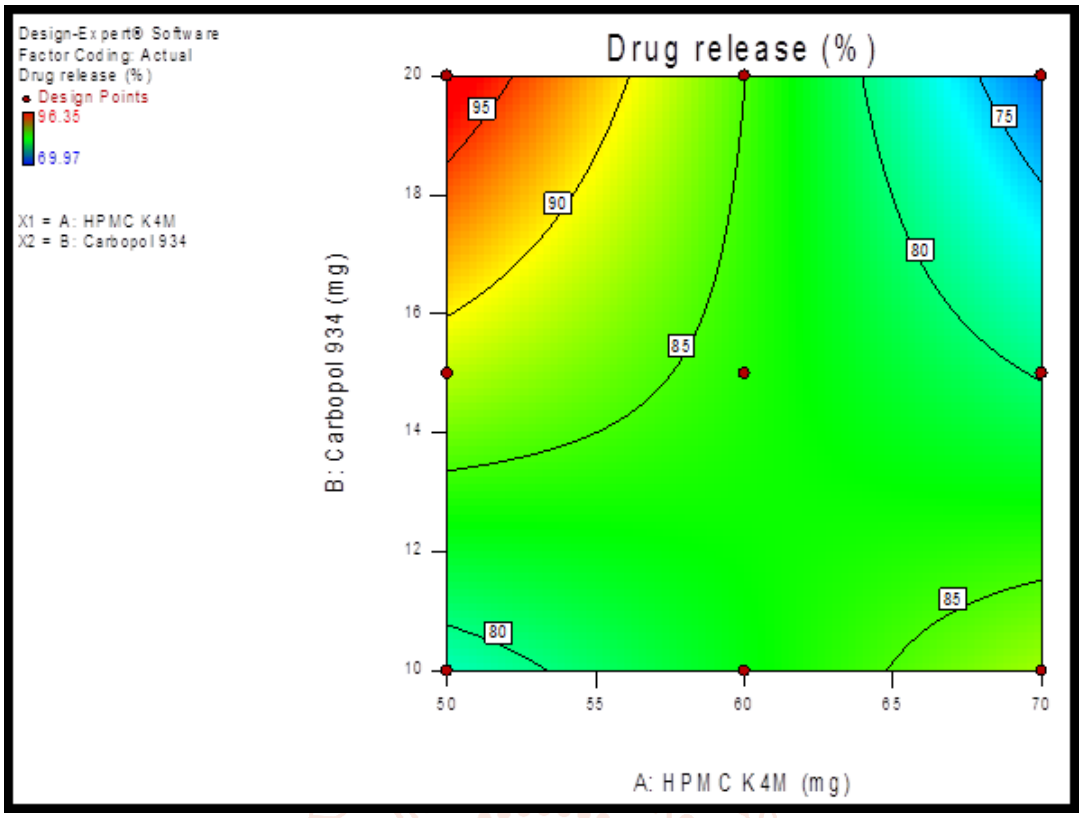

Figure: Contour plot showing effect of Carbopol 934 and HPMC K4M on drug release.

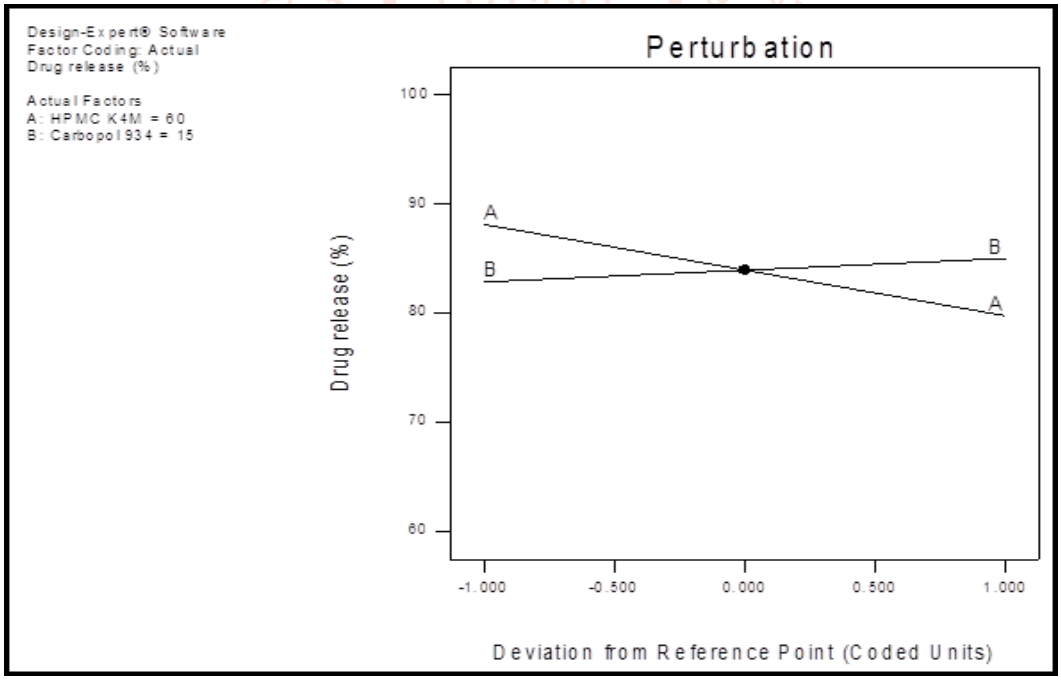

Figure: Perturbation plot showing effect of carbopol 934 and HPMC K4M on drug release

Table: Design Summary

Factor	Name	Unit	Type	Min	Max	-1 Actual	+1 Actual	mean	Std. Dev
A	HPMC K4M	mg	Numeric	50	70	-1.00	1.00	50	30.33
B	Carbopol934	mg	Numeric	10	20	-1.00	1.00	15	18.24

Table: Response summary for drug release

response	Name	Units	Obs.	Analysis	Minimum
Y1	Release	% drug released	9	Polynomial	71.15
Max.	Mean	Std. Dev	Ratio	Trans	Model
96.25	85.204	1.98	1.15	None	Linear

From Design expert version 11.0.0 optimum batch of HPMC K4M and Carbopol 934 mg was found to be optimized. Form this data F3batch was selected as optimized formulation.

Dissolution Kinetics:

In the present study, the drug release was analysed to study the kinetic of drug release mechanism. The results showed that the factorial design batches followed zero order and first order model kinetics, Higuchi and Connor's model kinetics and kosemeyer'speppas model kinetics.

Zero-order comparative evaluation model kinetics:

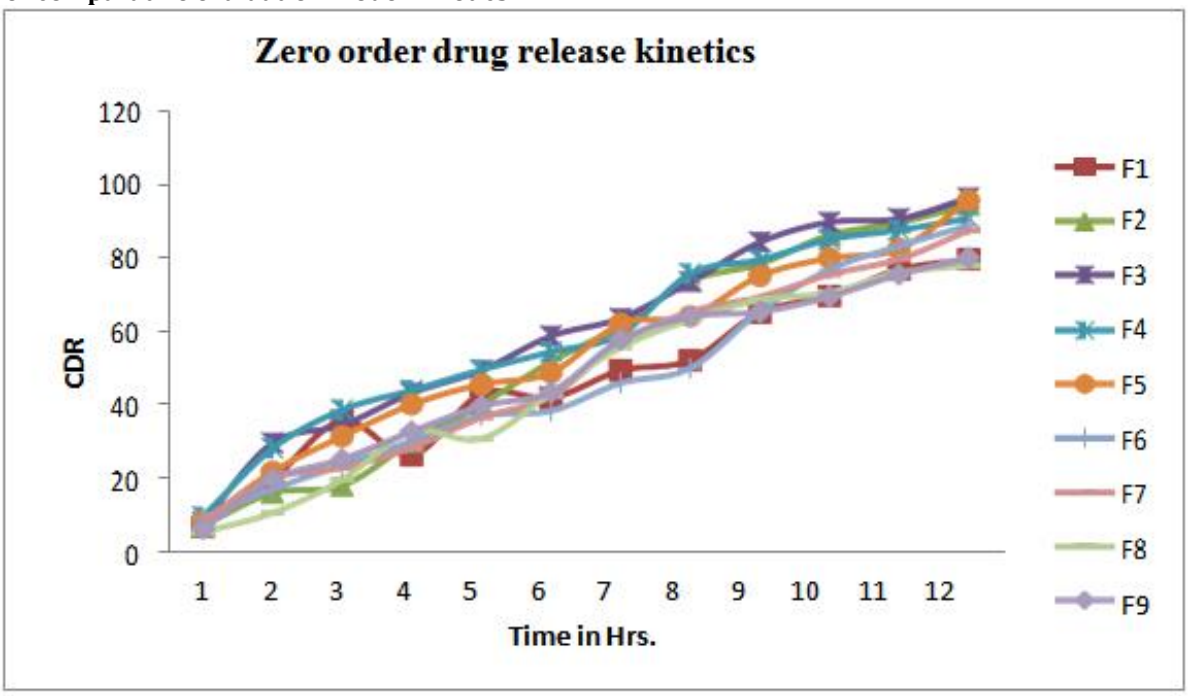

Figure Model graph for comparative evaluation of zero order release kinetics

Table: R^2 values for zero order release kinetics

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
R^2 value	0.9833	0.9807	0.9964	0.9885	0.9213	0.9774	0.9533	0.9940	0.9843

First-order comparative evaluation model kinetics

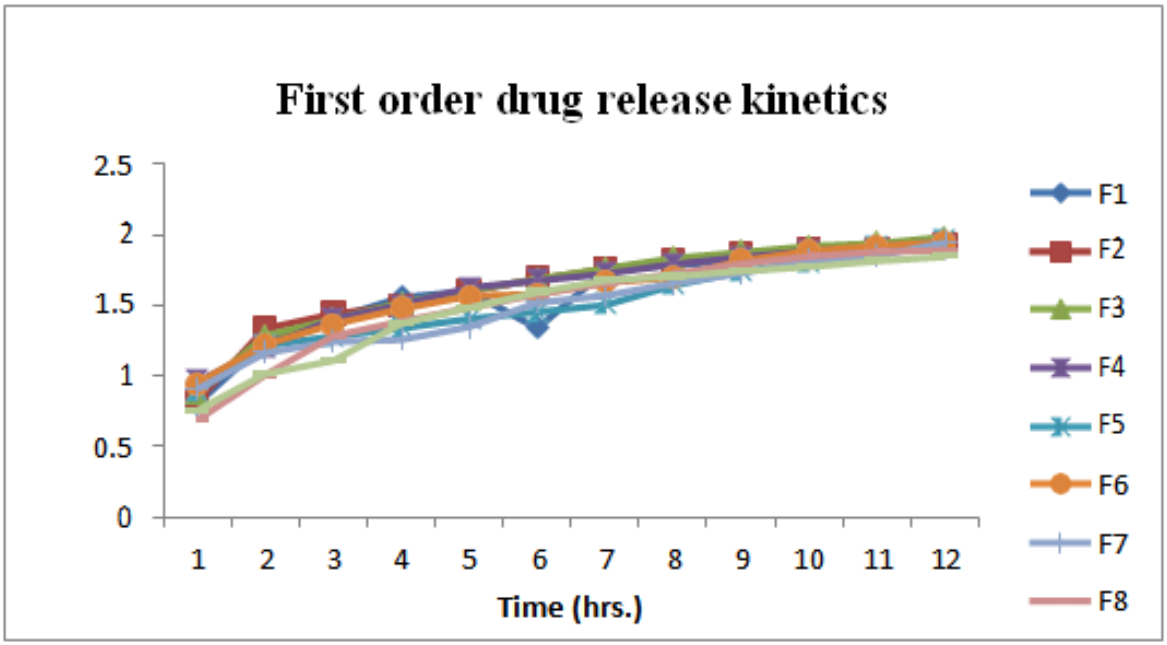

Figure: Model graph for comparative evaluation of First order release kinetics

Table: R^2 values for First order release kinetics

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
R^2 value	0.9894	0.9725	0.8538	0.9755	0.7646	0.8748	0.7994	0.9607	0.9882

Higuchi and Connor's model release kinetics:

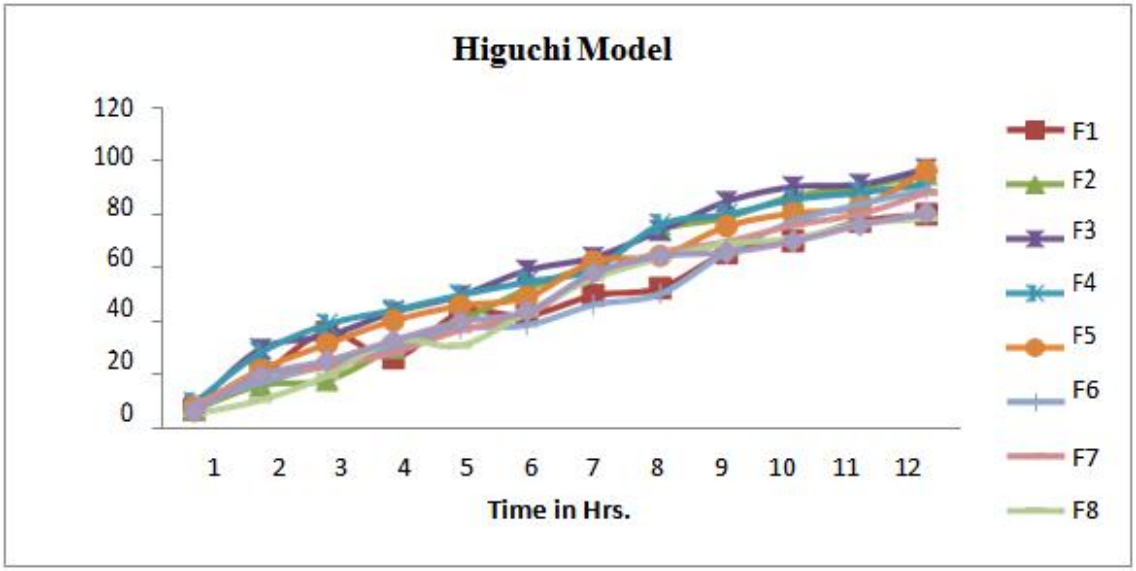

Figure: Model graph for comparative evaluation of Higuchi Connor's release kinetics

Table: R^2 values for Higuchi Connor's release kinetics

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
R^2 value	0.9965	0.985	0.976	0.9962	0.8365	0.9321	0.8673	0.9691	0.9772

Korsemeyer'speppas comparative evaluation model kinetics:

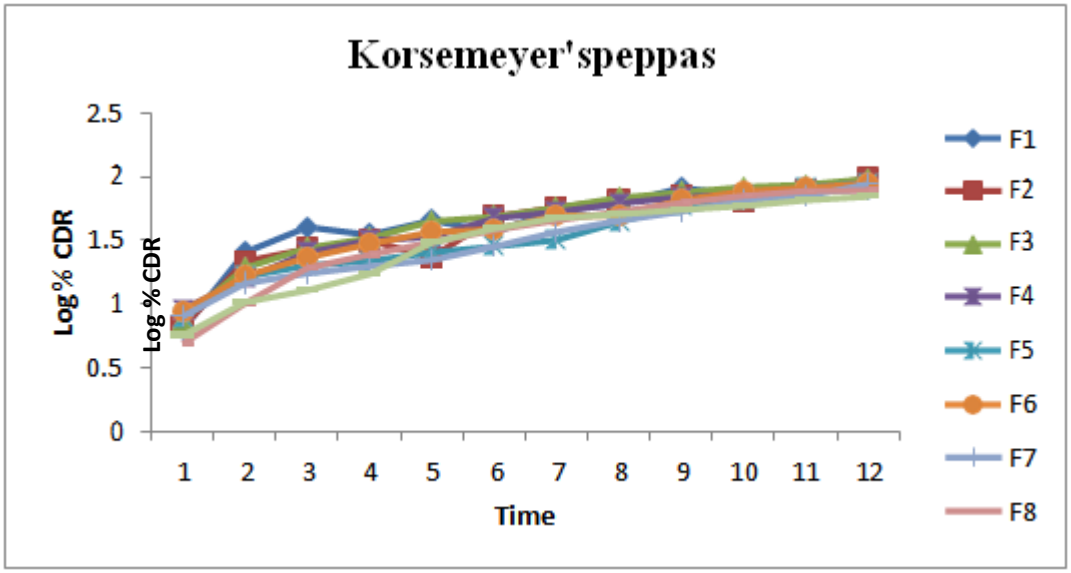

Figure: Model graph for comparative evaluation of Korsemeyer'speppas release kinetics

Table 33: R^2 values for Korsemeyer'speppas release kinetics

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
R^2 value	0.9806	0.9724	0.9943	0.9857	0.9293	0.9864	0.9404	0.9969	0.9835

Stability Studies:

The selected formulation were wrapped in aluminium foil and stored at 40 ± 2ºC and % RH 75% ± 5% temperature for 3 months. After 3 months the formulation F3were evaluated for the hardness, drug content and *in-vitro* % drug release. It was observed that there was no significant variation in the physical appearance, average weight, hardness and loss of drying after placing the tablets at various temperature and humidity conditions for a period of 3 months. Also the cumulative % drug release data showed that each of the formulation released a drug amount, within the limits laid down as per the ICH guidelines for stabilitystudy.

Table: Stability study for optimized formulation F3 at 40±2ºC+75% RH

Formulation code	1 month	2 month	3 month
F3	98.41 % ± 0.018	97.94 % ± 0.060	97.53 % ± 0.032

CONCLUSION:

The present study was carried out to develop the effervescent floating drug delivery of Dapagliflozin using HPMC K4M and Carbopol 934 polymers as the carrier. Dapagliflozin is BCS class III drug having high solubility and high permeability. Its oral bioavailability 55% and biological half-life is also approximately 12hrs. All the above reason are suitable for gastro retentive drug delivery system. After procurement of drug sample it was characterized for identification by FTIR. After identification check compatibility of drug with all excipient. It was found that it is compatible with all excipient there is no change in functional group. Physical property of Dapagliflozin tablet i.e. hardness, friability, average weight, thickness also complies with standard reference. Floating lag time of all nine formulation show within one minute total floating time was more than 12 hrs.

which are suitable for sustained release drug delivery system. The batch F3 shows 96.35% release in 12 hrs, so we concluded that rate of drug release increases in acidic environment of stomach. Release kinetic data of all the formulation show that F1-F9 formulation follows Korsmeyer-Peppas model. Stability study was conducted on tablets of batch F3 at 40±20C for 3 months.. From the discussion it was concluded that the Tablets of batch F3 was selected as optimum batch and evaluated for stability study.

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